Roche

Diagnostics

April 19, 2002

Docket No. 02D-0028
Dockets Management Branch (HFZ-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Dr. Jean Cooper,

Issues Analysis Report – FDA Proposed Cyclosporine & Tacrolimus 510(k) Review Criteria Guidance Document

Purpose

The purpose of this memo is to share with you the results of Roche Diagnostics' analysis of FDA's proposed cyclosporine or tacrolimus test kit 510(k) review criteria, and to ask for your review and consideration of our comments.

Introduction

On February 21, 2002, FDA published a draft cyclosporine and tacrolimus 510(k) review criteria guidance document as part of a notification of your intent to reclassify these devices. The public has been given until April 22, 2002, to submit comments to the Agency concerning the proposed guidance. The final version of this guidance document will serve as a special control for the devices when they are reclassified.

Reclassification

Roche Diagnostics fully supports your decision to reclassify the cyclosporine and tacrolimus devices. We share your confidence that the issuance of a 510(k) review criteria guidance document, as a special control, shall maintain the appropriate premarket regulatory oversight.

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Issues Analysis Report – FDA Proposed Cyclosporine & Tacrolimus 510(k) Review Criteria Guidance Document,
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510(k) review criteria comments

Roche Diagnostics examined the proposed 510(k) review criteria guidance and found four significant differences between the proposed method of evaluating a new assay's performance and Roche's traditional approach. These issues, presented as requests for modification or clarification of the proposed guidance are:

1. Permit manufacturers to use whole blood controls to evaluate an assay's imprecision and not require evaluating the imprecision at the limits of the reportable range as part of the same experiment.
2. Clarify that gathering multiple measurements from individual patients is not necessary to demonstrate substantial equivalence to a predicate device.
3. Allow manufacturers to use statistical analyses techniques that are linked to design input requirements in place of the technique described in the method comparison section of the guidance.
4. Eliminate the requirement that the manufacturer validate performance at laboratory sites other than that of the manufacturer.

Review request

We are pleased to submit these comments for your consideration. If your Agency revises the guidance document to incorporate our recommendations, Roche feels that manufacturers can consistently satisfy the Agency's 510(k) review criteria for cyclosporine and tacrolimus assays.

Kind regards,

Mike Flis
Regulatory Affairs Principal
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Enclosure

Precision Experiment

Issue

The proposed experimental design indicates the test's precision should be evaluated at levels near the limits of reportable range, using whole blood samples from patients taking cyclosporine or tacrolimus. The example given is "for an assay with a reportable range between 40 ng/ml and 400 ng/ml, appropriate levels for testing would be 40, 200, and 400 ng/ml."

The example implies that the testing should be performed at the absolute limits of the reportable range. This practice may be impractical since several samples shall produce test results falling outside the claimed limits, causing the manufacturer to discard this data.

The proposed experiment is more burdensome than the review criteria used in the assessment of PMA applications for cyclosporine assays. The PMA review criteria permitted manufacturers to assess their test's imprecision by repeatedly running whole blood control samples according to NCCLS guidelines EP5-A. The whole blood control samples were targeted to represent three levels: underdosed, therapeutic level, and overdosed.

The proposed experiment excludes the use of whole blood control samples and the example given implies the study must evaluate the test's precision at the absolute limits of the reportable range.

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Precision Experiment, Continued

Potential impact

This approach is inefficient and potentially more burdensome than FDA's previous PMA approval requirements. The following Roche COBAS INTEGRA Cyclosporine labeling claim, achieved through a PMA approval for a test with a reportable range of 17 to 500 ng/ml could not have been obtained using the proposed protocol.

BIO-RAD Lyphochek Whole Blood tri-level controls were assayed with the cassette COBAS INTEGRA Cyclosporine on the COBAS INTEGRA 700 analyzer according to NCCLS guidelines EP5-A (within run n=80, total n=80) to evaluate the assay reproducibility. The following results were obtained:

Within run	Level 1	Level 2	Level 3
Mean ng/ml	79.0	190.4	406.9
SD	4.32	4.49	19.8
CV %	5.5	2.4	4.9

Total	Level 1	Level 2	Level 3
Mean ng/ml	79.0	190.4	406.9
SD	7.07	11.2	31.2
CV %	9.0	5.9	7.7

Proposed resolution

We recommend evaluating a test's imprecision according to NCCLS guidelines EP5-A using whole blood control samples targeted at relevant drug levels.

Method Comparison Experiment

Issue 1

The guidance describes the possible use of multiple measurements from individual patients. The paragraph we question reads as follows:

"If you choose to include additional multiple measurements from individual patients, you should summarize your results of appropriate statistical analyses such as Analysis of Variance, Generalized Estimating Equations, or Bootstrapping, to account for correlation of repeat measurements within patients in the study. If multiple measurements from individuals are included they should range over time, post-transplant. FDA believes it is helpful for samples from patients undergoing various treatment regimens to be included, and therefore recommends including samples from multiple geographic sites or clinical centers."

This paragraph addresses more than one topic: the use of multiple measurements from individual patients and the benefits of drawing samples from multiple geographical sites or clinical centers. The final sentence applies to the method comparison study design in general, and should not be construed as only being pertinent to those manufacturers choosing to include multiple measurements from individual patients.

We are concerned that this paragraph could be misconstrued by some of the Agency's Scientific Reviewers as suggesting multiple measurements from individual patients should be a de facto 510(k) review criteria.

Potential impact

The inclusion of this paragraph might lead to the expansion of the 510(k) review criteria to include some form of a longitudinal study. Such a study should be unnecessary to demonstrate substantial equivalence to a currently marketed test system.

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Proposed resolution

We recommend moving the final sentence of this paragraph to the conclusion of the previous paragraph. That paragraph would read: Appropriate sample size depends on factors such as precision, interference, range, and other performance characteristics of the test. The number of patients should also be large enough so that inter-individual variation would be observed. A statistical justification to support the study sample size should be provided in the protocol description in the summary report. We expect that the sample size target, however supported, will include a minimum of 50 samples from 50 *individual patients* for each organ transplant group, for which the drug and test are indicated (i.e., a minimum of 100-150 samples total). FDA believes it is helpful for samples from patients undergoing various treatment regimens to be included, and therefore recommends including samples from multiple geographic sites or clinical centers.

What remains of the guidance document's proposed paragraph should be clarified to indicate that a multiple measurement from individual patients study is not necessary to demonstrate substantial equivalence and is only described in the guidance in case a manufacturer intends to summarize such a study in their proposed device labeling. To further distinguish this study from the required method comparison, we recommend moving this paragraph to the close of the method comparison section of the guidance.

Any manufacturer interested in summarizing a study involving multiple measurement from individual patients in their product labeling would consider the guidance provided, but it would be understood that this study would not be necessary to obtain 510(k) clearance.

Method Comparison Experiment

Issue 2	The guidance suggests separate analyses be performed for each organ transplant group for which the test is indicated and separate analyses, if the samples evaluated in the study include both trough and other times of blood draw, relative to drug administration. The results of these analyses must somehow contribute to an explanation of how the acceptance criteria for the method comparison study support substantial equivalence.
Potential impact	The proposed method of explaining acceptance criteria is overly restrictive and may in some cases be inconsistent with a manufacturer's design input requirements. A common IVD industry practice is to establish design input requirements based upon the desired relative agreement between the new assay an acknowledged reference methodology, as well as the more commonly utilized clinical laboratory method. The design specifications may specify analyses different than those described in the guidance document. The suggested method comparison data set analyses may impose specifications which may not be traceable to design input requirements, and thus not lend themselves to determining if the manufacturer's design input requirements have been met.
Proposed resolution	We recommend replacing the word "should" with the term "may" throughout this section of the guidance. The guidance should further indicate that the manufacturer may provide evidence that the acceptance criteria for the method comparison study meet their design input requirements as a means of supporting substantial equivalence. It should be noted that the guidance document describes one of what could be many acceptable approaches.

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Method Comparison Experiment, Continued

Proposed resolution, continued

Please consider the following revision to the proposed guidance:

In the 510(k) summary report, you should explain how the acceptance criteria for the method comparison study support substantial equivalence. There may be several viable approaches to accomplish this task. One approach may be to explain how the acceptance criteria for the method comparison study meet the product's design input requirements, specifically correlation to an acknowledged reference methodology as well as a more commonly used clinical laboratory method (the predicate device), as a means of supporting substantial equivalence. Another method is described below in greater detail.

You may conduct separate analyses of data for each organ transplant group for which the test is indicated. If samples evaluated in the study include both trough and other times of blood draw relative to drug administration, you may conduct separate analyses for these groups as well. When providing the results of the method comparison study, you should include the following information:

- Scatterplots of the new assay versus the reference (e.g., HPLC) method. The plots should contain all data points, the estimated regression line and the line of identity. Data points in the plot should represent individual measurements.
- A description of the method used to fit the regression line and results of regression analysis including, the slope and intercept with their 95% confidence limits, the standard error of the estimate (calculated in the y direction), and correlation coefficient may be included in the summary report. In cases where parameters are not consistent throughout the reportable range, estimates of more than a single range may be appropriate. If the comparator, as well as the new assay is subject to measurement error, a regression method such as the Deming method may be appropriate, rather than Least Squares [19].
- To illustrate the degree of inter-individual variations, you may include graphs of difference in measurements (i.e., new device minus reference HPLC method) versus the reference HPLC method. Appropriate representations include a bias plot of difference in measurements (y - x) versus the reference method (x), as recommended in NCCLS EP9 [20], or versus the mean of y and x, as recommended by Bland and Altman [21].

If you are submitting a traditional 510(k), you may also choose to include line data, if this would be beneficial for clarification of the protocol or results.

Studies at external sites

Issue

The proposed guidance suggests that the manufacturer should validate performance at laboratory sites other than that of the manufacturer. FDA recommends that the manufacturers include this validation, at two external sites, as part of the method comparison study.

Potential impact

Imposing this requirement on all manufacturers may increase the costs and complexity of performing the method comparison study in a timely manner. In some cases, manufacturers may have access to appropriate samples within their facility, making it unnecessary to perform the method performance specification study at facilities other than that of the manufacturer. In cases such as this the manufacturers should be permitted to submit data collected in their own facility to validate the method performance specification. Although many manufacturers may choose to validate performance at laboratory sites other than that of the manufacturer, all manufacturers should not be required to follow this approach.

The tests described in this guidance document are regulated under CLIA as either moderate or high complexity tests. The CLIA regulations impose requirements on the laboratory to establish and verify the method performance specifications prior to reporting patient test results. According to 42 CFR 493.1213(b)(1), "each laboratory that introduces a new procedure for patient testing using a device cleared by the FDA as meeting certain CLIA requirements for quality control, must demonstrate that, prior to reporting patient test results, it can obtain the performance specifications for accuracy, precision, and reportable range of patient test results, comparable to those established by the manufacturer."

The CLIA regulations provide adequate incentive to the manufacturers to establish performance specification labeling claims that can be reliably achieved by their lab customers. If a manufacturer fails to establish performance specifications that can be achieved by their lab customers, those lab customers shall reject the product before reporting any patient results. The manufacturer shall lose credibility with his customers.

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Studies at external sites, Continued

Proposed resolution	Since the CLIA regulation protects the public against the possibility of the manufacturer establishing method performance specification that can not be replicated in the real world, there is no cause for the FDA to implement this 510(k) requirement. We recommend removing this requirement from the guidance document.